Overview of Establishment Registration and Product Listing Final Rule

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Focus Today

- Specific provisions of the regulation
  - 1271 Subpart A and B requirements
  - Definitions
- Logistics with registration and listing
  - Who? What? When?
- Status of registrations

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): Establishment Registration and Product Listing

- Proposed in 1998
- Finalized in 2001
- Effective in 2001 for establishments regulated under previous rule – 21 CFR Part 1270 – musculo-skeletal, ocular and skin
- Effective in 2004 for newly regulated establishments – hematopoietic stem cells and reproductive tissues

Implementation

- All HCT/P establishments were required to register and list by March 29, 2004
- Exception made if the establishment only manufactures human heart valves and dura mater (currently medical devices) - until May 25, 2005
- Registration does not constitute a determination that an establishment is in compliance with the regulations –this is determined during a facility inspection

Final Rule: Registration and Listing

- Subpart A and B of 21 CFR Part 1271
- Provides purpose and scope for all parts of the regulation
- Important definitions
- Criteria that need to be met to be regulated solely under section 361 (without pre-market approval)
- Exceptions from registration
- Procedures for registration and listing

Subpart A and B

- Purpose: Create a unified registration and listing system for all establishments that manufacture HCT/Ps
- Manufacture
  - Any or all steps in the recovery, processing, storage, labeling, packaging, or distribution, and
  - Screening and testing of the cell or tissue donor (communicable disease testing)

Definitions

- **Establishment**: A place of business under one management, at one general physical location that engages in the manufacture of HCT/Ps, includes:
  - Individual, partnership, corporation, association, or other legal entity and,
  - Facilities that engage in contract manufacturing services for a manufacturer.

Definitions

- **HCT/P** means articles containing or consisting of human cells or tissue that are intended for implantation, transplantation, infusion or transfer into a human recipient.
- **Distribution** means any conveyance or shipment of an HCT/P that has been determined to meet all release criteria, whether or not it is entirely intrastate. If an entity does not take physical possession of an HCT/P, the entity is not considered a distributor.

Definitions

- **Recovery** means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.
- **Storage** means holding HCT/Ps for future processing and/or distribution.
- **Processing** means any activity performed on an HCT/P other than recovery, donor screening and testing, storage, labeling, packaging, or distribution.

Conforming Amendments

- Modified 207.20 registration and listing for producers of drugs and listing of drugs in commercial distribution
- Modified 807.20 registration and listing for manufacturers and distributors of devices
- If the establishment manufactures an HCT/P considered a drug (biologic) or device, they must now follow the 1271 procedures for registration and listing

Implementation Continued

- Establishments manufacturing medical devices considered HCT/Ps must now register and list per 1271
  - 65 medical device registrations identified and notification letters sent
- Establishments previously listing hematopoietic stem cells as a blood product must now register and list per 1271
  - 86 blood registrations identified and notification letters sent

1271.10 Criteria for Regulation Solely under Section 361

All 4 criteria must apply – if an HCT/P does not fit all, then it is regulated as a biological product or medical device:

1. Minimal manipulation
2. Homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent
3. Not combined with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent that do not raise new clinical safety concerns with respect to the HCT/P and

1271.10 Continued

4. Either:

a. does not have a systemic effect and is not dependent on the metabolic activity or:

b. Has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and

-Is for autologous use;

-Is for allogeneic use in a 1st or 2nd degree blood relative or

-Is for reproductive use

More Definitions

- **Minimal Manipulation** means:
  - For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and
  - For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.
- **Homologous use** means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

Exceptions from Registration – 1271.15

- Use of HCT/Ps solely for nonclinical scientific or educational purposes
- Removing HCT/Ps from an individual and implanting them into the same person during the same surgical procedure
- Carriers who accept, receive, carry or deliver HCT/Ps (e.g. FedEx, UPS)

More 1271.15 Exceptions

- Does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for use within your facility
- Only recovers reproductive HCT/Ps for immediate transfer into the sexually intimate partner of the donor
- Individual who solely recovers HCT/Ps under contract or other agreement with a registered establishment (other requirements apply)

1271.20 - HCT/Ps That Don't Fit!

- If an HCT/P does not meet the 4 criteria for regulation under section 361 of the PHS Act
- Then it is regulated as a drug, device, and/or biological product (ex. Carticel)
- Requires pre-market approval
- No registration/listing is required until the HCT/P is licensed, approved or cleared for marketing

Registration Logistics:When

- Form 3356 – 30 minutes to complete
- Must register within 5 days after beginning operations
- Required annually in December - mail, fax or web-based
- Amend within 5 days if the ownership or location of the establishment changes
- Amend within 6 months if other changes

Initial Registration

- FDA/CBER receives form and enters data in the Human Cell and Tissue Establishment Registration (HCTERs) data base
- Copy of form is sent to FDA district office.
- District office will verify that the firm is in operation and is required to register
- District office generates and sends FEI registration number to CBER
- CBER sends validated Form 3356 to establishment and district office with the registration number

Annual Registration

- Establishments notified by CBER in November
- Establishments must return signed and dated form by end of December
- If information changed – entered into HCTERS
- New form with new validation date sent to establishment and the district office

Electronic Registration

- On line registration available since August 2003
- Easy to Use – FDA encourages use, on line instructions and link to help email
- Can be used for initial, annual, changes and inactivation
- FDA may possibly require that all registrations be submitted electronically in the future
- Great if you have multiple establishments to register – user profile reduces information that has to be entered
- Can save and submit at later date if need more information

What Information is Needed

- Specifics on address and phone number of physical location
- Specifics on reporting official – signed and dated – address, phone, email address
- Indicate manufacturing functions – screen, test, process, distribute etc
- Indicate all HCT/Ps involved in any manufacturing function – include proprietary names
- Indicate if HCT/P is “361” or “351” and regulated as biological drug or device

International Establishment Registrations

- Required if distributing HCT/Ps in the US
- Need to identify a US based agent
  - Provide address and phone number
  - Foreign establishment is not required to notify their US agent when shipping products
- Responsibilities of US agent include assisting FDA with communications concerning products and in scheduling inspections
- Future compliance with BioTerrorism Act – may require electronic listing of all consignees

Problems Observed in Filling Out Form 3356

- Products listed as both 361 and 351 HCT/P
- No reporting official's information including signature/date
- All various sizes/shapes of bone listed
- Heart valve and dura mater checked under 361 HCT/P category
- Test labs list products - only need to check function - test donors not products
- Multiple registrations from the same address

Who Must Register?

- Blood bank stores purchased bone and ships to another institution for use
- Hospital stores tissue from a patient in case the surgeon needs it for another patient
- Satellite location across town where manufacturing is done
- Hospital gas sterilizes bone for further use
- Test laboratories that test specimens from organ donors, and the results are used to determine eligibility of tissue donors

Who Must Register?

- Testing lab that performs donor testing for communicable diseases
- Organ procurement organizations that procure tissue or screen and/or test donors for registered establishments
- Foreign procurement sites that supply tissue for import to the US
- Hospital with stem cell, fertility and surgical bone bank facilities – 1 registration not 3

Who Does Not Register?

- Supplies tissues only for non-clinical research or educational use
- Building used only to store procurement kits-site under control of a registered facility
- Transfusion service stores tissue only for their own hospital's surgeries
- Distribution/broker who only facilitates distribution but does not take physical possession of the HCT/P

Who Does not Register?

- Testing laboratory that only performs chemical or microbiological testing for donor tissue
- Sales individuals under contract to registered establishment and who don't distribute HCT/Ps
- Employees of a registered establishment that work out of their homes and who only recover

Registration Current Status

- Human Cells and Tissues Establishment Registration (HCTERs) Database
- 1594 establishments currently registered
  - 629 musculo-skeletal, ocular, skin
  - 567 hematopoietic stem cells
  - 360 reproductive tissues/cells
  - 20 somatic cells
- Includes 137 foreign establishments – mostly list only hematopoietic stem cells

of Establishments Listing Each Product

Bone	485	HeartValve	174	Somatic Cells	68
Cartilage	233	Ligament	241	Tendon	264
Cornea	163	Oocyte	294	Cord Blood Stem Cells	144
Dura Mater	15	PBS Cells	381	Vascular Graft	171
Embryo	312	Sclera	141	Amnion	11
Fascia	253	Semen	370		

of Establishments Listing Each Function

Recover	887
Screen	749
Test	607
Package	591
Process	797
Store	1119
Label	743
Distribute	906

Establishments by FDA District Office

New England	65	Florida	91	New Orleans	89
New York	79	Chicago	54	Kansas City	71
San Juan	7	Cincinnati	56	Denver	45
New Jersey	41	Detroit	56	Los Angeles	118
Baltimore	76	Minneapolis	71	San Francisco	78
Philadelphia	60	Int. Op. Group	129	Seattle	51
Atlanta	75	Dallas	118		

Registration Information Available

- Website at www.fda.gov/cber/tiss.htm
  - Published documents/Q and A's
  - Registration information – including Form FDA 3356 and electronic access
  - New public query for information on registrants
- E-mail address for registration questions tissuereg@cber.fda.gov